

Sulfolane Reference Doses

TERA Peer Review of
Sulfolane RfDs Meeting
September 16, 2014

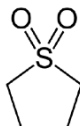


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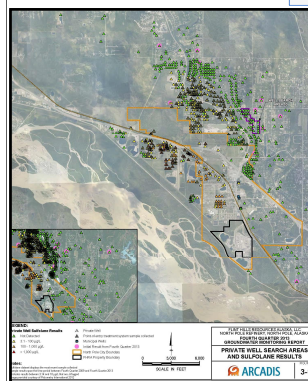
What is sulfolane?

Property	Value
Molecular weight	120.18
Freezing point	27.4 – 27.8 °C
Specific Gravity (50/20 °C)	1.265
Vapor Pressure (25 °C)	0.0042 mm Hg
Henry's Law constant	4.6 X 10 ⁻⁶ atm·m ³ /mole
Solubility in water (25 °C)	2100 g/L



- Industrial solvent used during gasoline production
- Used to separate aromatic compounds from hydrocarbon mixtures and to purify natural gas
- Low vapor pressure
- Highly soluble in water
- Not well absorbed through skin

Sulfolane in North Pole, Alaska



- Sulfolane discovered in private drinking water wells in 2009
- Alternative water supplies
- Current sulfolane plume approx. 2.5 miles wide by 3 miles long.

Why an Expert, Peer-Review?

- Developing a cleanup level involves many steps. For DEC, the reference dose is a key component in the calculation that determines a cleanup level.
- To ensure the most scientifically sound groundwater cleanup level for sulfolane, DEC is seeking the panel's expert, independent recommendation on the oral, chronic reference dose.

Key Studies

Zhu et al. 1987

- 6-month study in guinea pigs
- Hepatic effects, change in cell counts, dispersion of spleen white pulp
- No effect level = 0.25 mg/kg-d

Huntingdon Life Sciences 2001

- 13-week study in rats
- Reduction in lymphocytes, monocytes, LUC counts in females
- No observed effect level = 2.9 mg/kg-d

Zhu et al. 1987

- Acute toxicity in mice, white rats, and guinea pigs

Species	LD ₅₀
Mice	2504mg/kg
Rats	2343mg/kg
Guinea pigs	1445mg/kg

- 90-day study in white rats and guinea pigs
 - Guinea pigs were more sensitive to sulfolane than rats
- 6-month study in guinea pigs**
- Mutagenicity Test (Ames, mice marrow erythrocyte micronucleus, SCE assay)
- Teratogenicity test

Zhu et al. 1987 – 6 month toxicity study

- Guinea pigs – 40 each dose group, equal numbers male/female
- Dose groups: 0.25, 2.5, 25, 250 mg/kg and control
- Biochemical and pathological evaluations
- Change rates in fatty deposits showed dose-response relationship
- Dose groups 2.5, 25 and 250 mg/kg
 - Fatty deposits change in the liver tissue
 - Shrinkage of spleen white pulp
 - Decreasing cell counts in spinal marrow
- Authors noted:
 - Chronic threshold at 2.5 mg/kg
 - No effect dose at 0.25 mg/kg

Huntingdon Life Sciences, 2001

- 13-week exposure in drinking water
 - CD rats, 20 animals per dose group (10 males/10 females)
 - Good Laboratory Practices
 - Battery of tests conducted
 - Males – hydrocarbon nephropathy at 400 mg/L or more
 - Females – reduced lymphocytes, monocyte, LUC counts at 100 mg/L or more
 - Not seen in males
 - No observed effect level = 8.8 mg/kg-d for males and 2.9 mg/kg-d for females

DW conc. (mg/L)	0	25	100	400	1,600
Male dose (mg/kg-d)	0	2.1	8.8	35.0	131.7
Female dose (mg/kg-d)	0	2.9	10.6	42.0	191.1

Available Sulfolane RfDs

Source	Principal Study	Test Species	Endpoint	Modeling Approach	Point of Departure (mg/kg-day)	Composite Uncertainty Factor	Reference Dose (mg/kg-day)
CCME, 2006	HLS 2001	Rat (female)	WBC counts	NOAEL	NOAEL = 2.9	300	0.0097
ATSDR, 2010	Zhu et al. 1987	Guinea pig	Hepatic effects, changes in serum ALP, WBC counts	NOAEL	NOAEL = 0.25	100	0.0025
ATSDR, 2011	Zhu et al. 1987	Guinea pig	Dispersal of spleen white pulp	BMD	BMDL ₁₀ = 1.5	1,000	0.002
TCEQ, 2011	HLS 2001	Rat (female)	WBC counts	BMD	BMDL ₁₀ = 16.1 BMDL ₁₀ = 3.9	300	0.013
US EPA, 2012	HLS 2001	Rat (female)	WBC counts	NOAEL	NOAEL = 2.9	3,000	0.001
Magee, 2012	HLS 2001	Rat (female)	WBC counts	BMD	BMDL = 11.64	1,000	0.01
Thompson et al., 2013	HLS 2001	Rat (female)	WBC counts	BMD	BMDL ₁₀ = 16 BMDL ₁₀ = 3.9	300	0.01
Health Canada, 2014	HLS 2001	Rat (female)	Lymphocytes	BMD	BMDL ₁₀ = 4.12	1,000	0.00412

Uncertainty Factor Differences

Source (By Date)	UF _A	UF _D	UF _H	UF _L	UF _S	UF _C
CCME, 2006	10	3*	10	--	--	300
ATSDR, 2010	10	--	10	--	--	100
ATSDR, 2011	10	--	10	--	10	1,000
TCEQ (Harvey), 2011	--	3	10	--	10	300
US EPA, 2012	10	3	10	1	10	3,000
Magee, 2012	10	--	10	--	10	1,000
Thompson et al., 2013	3	3	3	--	10	300
Health Canada, 2014	10	10	10	--	--	1,000

Notes:
 * Based on the CCME application of uncertainty factors, this value was used to account for adequate, but not extensive dataset; subchronic-chronic extrapolation; and serious effects concerns (CCME 2006).

Questions